REMARKS/ARGUMENTS

Applicants will respond to the various items in the office action in the order they are presented.

Initial Comments on Claim Formatting

The examiner has correctly noted that newly submitted claims 13-15 contained spurious underlinings. The claims have been amended to remove the underlinings.

Claim Objections

Claim 12 has been objected to because of a spelling/typographical informality. The intent was to use the word "many" and the claim has been so amended.

Claim Rejections - Obvious Type Double Patenting

The Examiner has rejected claims 1, 3, 4, 7, 8, and 11-15: "...under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-7 of U.S. Patent No. 6,185,506." As applicants noted in their prior response: "Applicants acknowledge this rejection and will timely file a terminal disclaimer once claims in the present application have otherwise been allowed." Accordingly, accompanying this Response Applicants present a Terminal Disclaimer with a check for the required fee.

Claim Rejections- 35 U.S.C. § 101

The Examiner has rejected claims 3 – 4 and claims 12 - 13 under 35 U.S.C. § 101 "...because the claimed invention is directed to non-statutory subject matter." For purposes of discussion, the Examiner's statement is set out below with inserted numerals to serve as reference for Applicants' response:

Claims 3, 4, 12 and 13 are drawn to computer implemented methods of characterizing a three dimensional structure. **[1]**The steps of the method result in "generating the CoMFA steric fields for each aligned molecular side chain." The generated CoMFA steric field is not a concrete, tangible and useful result according to MPEP 2106. This steric field is a piece of data which must further be interpreted and manipulated by the end user. **[2]**According to the specification at page 36, CoMFA steric fields are a description of the differences between structures aligned by "overlaying the atoms that lie within some selected common substructure and arranging the other atoms according to a unique canonical rule with any resulting steric collisions ignored." **[3]**The specification continues in that these differences are further used *as part of a process* to select molecules from a set that are either similar or dissimilar. The CoMFA steric field value by itself does not appear to have specific meaning or usefulness. The step of selecting similar or dissimilar entities based on this value is not present in the rejected claims. **[4]**Pages 42-43 of the specification discuss the computation of the CoMFA steric field value. It is a numeric value which represents a difference of atom positioning of a "reactant" in comparison to an "alignment template." This numeric value on its own has no intrinsic meaning. It must be further compared with or applied to other values to provide a meaningful result. (See for example Table 1, and corresponding explanations - the meaningful values of the table are *ratios* and *comparisons* of CoMFA values across a data set, not for a single value.)

In computational chemistry a molecular structural descriptor is a description of a molecule or molecular part which characterizes the molecule or molecular part in such a way that that molecule or molecular part can be usefully compared to another molecule or molecular part. Prior to the present invention, many molecular structural descriptors were known in the literature which claimed to characterize the three dimensional shape of a molecule or molecular part. However, no method of determining the validity of those descriptors existed. Part of the teaching of the present application is of a method of validating such descriptors. The application further teaches that the CoMFA steric fields about a

molecular part(side chain) that has been aligned in a standardized manner is a valid descriptor, that is; it describes the three dimensional structure in such a way that it can be used to compare the shapes of different molecular parts.

[1] Applicants respectfully disagree with the Examiner's characterization that the field values about a topomerically aligned side chain are not concrete, tangible and useful results that meet the section 101 requirements. In fact, the field values constitute a complete three dimensional description of the shape of a side chain. The fact that the shape of the side chain (represented by the field values) can further be used to compare the shapes of different side chains, does not mean that the representation of the molecular shapes does not stand on its own or has to: "...be further interpreted and manipulated by the end user." The shape of each side chain represented by the field values is well understood by those in the art to be a three dimensional molecular structural descriptor appropriate to the side chain. In this regard and as will be discussed below, Table 1 in the specification compares the results of using the field values as shape descriptors across a whole range of biological activites to demonstrate that the descriptor is valid.

[2] Applicants respectfully disagree with the Examiner's characterization that the steric field values are themselves: "...a description of the differences between structures..." Applicants submit that the Examiner has misunderstood the cited part of the disclosure. Since the steric field values describe the three dimensional shape of the side chains, those values can be used to compare the three dimensional shapes of different side chains. As taught in the specification, the differences in field values between different side chains, is a measure of the difference in shape of the side chains.

[3] To the extent that the field values can be used in a selection process to find similar or dissimilar molecular shapes, the Examiner's statement is correct. However, Applicants respectfully submit that the Examiner is in error when stating that the steirc field value by itself does not appear to have specific meaning or usefulness. The field values represent the shape of the side chain. Unlike the story of the blind men arriving at different descriptions of what an elephant must look like as a result of touching different parts of the elephant, the field values

describe (without further modification or processing) the full three dimensional shape of each topomerically aligned side chain.

[4] Applicants respectfully submit that they do not understand the Examiner's citation to: "It is a numeric value which represents a difference of atom positioning of a 'reactant' in comparison to an 'alignment template'." Applicants can not identify the reference in the cited pages 42-43. The only reference to "template" has to do with reducing the steric field contribution of those atoms located some distance away from the template-matching atom. Applicants also respectfully submit that the Examiner is in error in suggesting that the field values must be compared or applied to other values to provide a meaningful result. As support for this interpretation, the Examiner points to Table 1 and the corresponding explanations to suggest that: "...the meaningful values of the table are *ratios* and *comparisons* of CoMFA values across a data set, not for a single value." Applicants submit that this is not the point of Table 1.

A molecular structural descriptor to characterize the three dimensional shape of a molecule or molecular part is generally useful only if it can be employed with all different types of molecular structures. For instance, it may be hypothetically possible to construct a descriptor for molecular structures active in a particular biological assay. However, such a descriptor might be totally useless when characterizing molecular structures active in a different biological assay. The only way to know if a given descriptor is generally useful across a whole range of molecular structures is to apply that descriptor across a range of molecular structures associated with different activities. This validation procedure is outlined starting on page 45 of the specification. Table 1 reports how the steric field metric around topomerically aligned molecular structures performed in the Patterson Plot tests that determine validity of the descriptor. Table 1 does not teach that steric field description of molecular shape is not meaningful for a single value but only across a data set as suggested by the Examiner. The table actually clearly shows that the descriptor is valid for characterizing the shape of molecular structures that interact at a variety of ligand-protein activities.

Finally, the addition of the refinement of adding the hydrogen bonding field

information to the steric field information does not make the shape representation of the side chain contained in the field values any less useful. Attached to this Response is a graphic created by one of the inventors for presentation of the topomeric alignment technology. The graphic is pretty much self explanatory of the process. It is included because section "D" shows what has been discussed. While the printout is not perfect, one can see the topomerically aligned molecular structure embedded within the three dimensional matrix of grid points represented by the + signs. The shaded portions represent the intensity of the steric field at points within the grid, the darker portion having a higher intensity. Clearly the shaded portions (field values) represent the three dimensional shape of the molecule.

For all the reasons set forth, Applicants respectfully submit that the claims recite statutory subject matter. Applicants respectfully request the Examiner to remove the rejections of record.

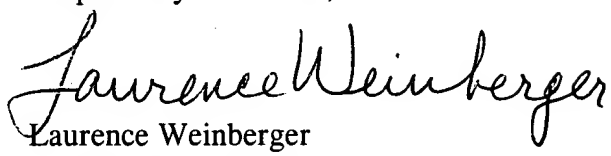
Claim Rejections- 35 USC § 112, second paragraph

The Examiner has rejected claim 11 under 35 USC § 112, second paragraph as being indefinite since the metes and bounds of claim 11 are unclear. In particular, the Examiner has cited the expression: "enabling comparison between the side chains of shape related properties." The Examiner has correctly interpreted what Applicants' intended by the language of the claim, namely of "enabling comparison of the shape related properties of the side chains." Applicants have amended claim 11 accordingly. Applicants respectfully submit that the claim as amended meets the requirements of 35 USC § 112, second paragraph and request the Examiner to remove the rejections of record.

Applicants submit that they have adequately addressed all grounds for rejection raised by the Examiner, and respectfully request that a timely Notice of Allowance be issued in this case.

February 17, 2005

Respectfully submitted,



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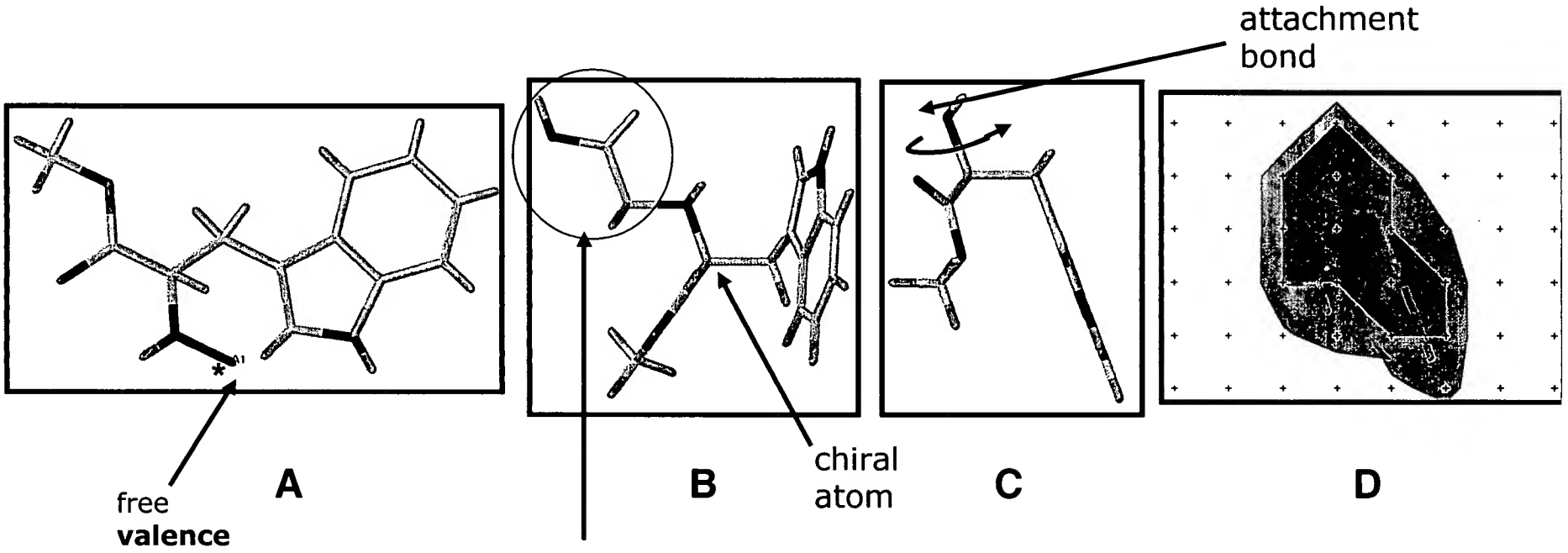
Generating a Topomer



A => B: Attach "anchor group";

generate 3D model;

overlap attachment bond

B => C: starting at attachment bond:

adjust chirality

select torsion end-points and adjust dihedral angles